Complete Summary

GUIDELINE TITLE

Radiotherapy for newly diagnosed malignant glioma in adults.

BIBLIOGRAPHIC SOURCE(S)

Neuro-oncology Disease Site Group. Laperriere N, Perry J, Zuraw L. Radiotherapy for newly diagnosed malignant glioma in adults [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Jan [online update]. 25 p. (Practice guideline report; no. 9-3). [80 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Newly diagnosed malignant glioma

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Neurology
Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate the role of radiotherapy in adult patients with newly diagnosed malignant glioma
- To evaluate the optimal radiotherapy characteristics, if it is to be offered

TARGET POPULATION

Newly diagnosed adults with histologic confirmation of the following diagnoses:

- Glioblastoma multiforme
- Malignant astrocytoma
- Malignant astrocytoma grade 3
- Malignant astrocytoma grade 4
- Malignant glioma
- Gliosarcoma

INTERVENTIONS AND PRACTICES CONSIDERED

Conventional Radiation (versus no radiation)

1. Whole brain versus regional field radiation
2. Different radiation doses

The following are considered but not recommended as standard care:

1. Hyperfractionated radiotherapy
2. Accelerated radiotherapy
3. Hypofractionation
4. Brachytherapy
5. Hyperthermia
6. Particle therapy
7. Radiosensitizers
    - Hypoxic cell sensitizers (metronidazole, misonidazole, ornidazole)
    - Halogenated pyrimidines
8. Radiosurgery

MAJOR OUTCOMES CONSIDERED

- Survival
- 1-year mortality rates

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Original Guideline: September 2000

MEDLINE (1966 to April 2003), CANCERLIT (1983 to October 2002), and the Cochrane Library (2003, Issue 1) databases were searched with no language restrictions. "Glioma" (Medical subject heading [MeSH]) was combined with "radiotherapy" (MeSH), "radiotherapy dosage" (MeSH), "dose fractionation" (MeSH), "brachytherapy" (MeSH), "radiation-sensitizing agents" (MeSH), "radiosurgery" (MeSH), and each of the following phrases used as text words: "hypofraction:", "hyperfraction:", "accelerated", "particle". These terms were then combined with the search terms for the following study designs or publication types: practice guidelines, meta-analyses, and randomized controlled trials. To identify non-randomized studies when no randomized trials were available, the search was repeated using all search terms except the study design terms described above. A search of the proceedings of the 1997 through 2002 meetings of the American Society of Clinical Oncology (ASCO) and the 1998 to 2002 meetings of American Society for Therapeutic Radiology and Oncology (ASTRO) was also conducted. The Physician Data Query (PDQ) database: (http://www.cancer.gov/search/clinical_trials/) was searched for reports of ongoing clinical trials. Relevant articles and abstracts were reviewed and the reference lists from these sources were searched for additional trials.

January 2004 Update

The original search has been updated using MEDLINE (through January 2004) and the Cochrane Library (2003, Issue 3) databases. Abstracts published in the proceedings of the annual meetings of American Society of Clinical Oncology (through 2003) and American Society for Therapeutic Radiology and Oncology (1997 to 2003) were systematically searched for evidence relevant to this evidence summary.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

- Meta-analyses and randomized trials comparing various aspects of radiotherapy in patients with malignant glioma
- Where no randomized trials were available, non-randomized studies were reviewed.
- Abstracts of trials were also considered.
- The outcome of interest was survival.

NUMBER OF SOURCE DOCUMENTS

Original Guideline: September 2000

Conventional radiation versus no radiation -- 6 studies
Radiation volume -- 2 studies
Radiation dose -- 2 studies

Hyperfractionated radiotherapy -- 7 studies + 1 meta-analysis
Accelerated radiotherapy -- 5 studies
Hypofractionated radiotherapy -- 7 studies
Brachytherapy -- 2 studies
Hyperthermia -- 1 study
Particle therapy -- 5 studies
Sensitized radiation -- 13 studies + 2 meta-analyses
Radiosurgery -- 11 studies

January 2004 Update

New evidence is available from three randomized controlled trials.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Original Guideline: September 2000

One-year mortality data from the trials of postoperative radiotherapy versus no postoperative radiotherapy, and the trials of hyperfractionated radiotherapy versus conventional fractionation radiotherapy, were pooled in separate meta-analyses using the software package Metaanalyst[0.998] (J. Lau, Boston, MA, USA).Reported figures or estimates obtained from tables or graphs were used. For the calculation of survival, the total randomized population was included in the denominator, based on intention-to-treat, unless the only available data were for the evaluable patients. The random effects method was used as the more conservative estimate of effect. The pooled results were examined for statistically significant heterogeneity ($p<0.10$). Results were expressed as risk ratios (RR), where an RR less than 1.0 favours the experimental group and an RR greater than 1.0 favours the control group.

January 2004 Update

New evidence is available from three randomized controlled trials. The guideline authors have reviewed this evidence and concluded that it is consistent with the original guideline recommendations.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Disease Site Group Consensus Process

The Neuro-Oncology Disease Site Group (DSG) reviewed the evidence and developed recommendations to address the following clinical questions: 1) What is the role of radiotherapy in adult patients with newly diagnosed malignant glioma? 2) If radiotherapy is offered, what are the optimal radiotherapy characteristics? This practice guideline report has been reviewed and discussed by the Neuro-Oncology DSG on several occasions and was approved with the addition of the following general comments.

Many of the studies discussed in this systematic review were performed over the last two to three decades. There have been major technological advances in both the delivery of radiotherapy and in diagnostic imaging in the last five to ten years, such that results and recommendations based on these older data may no longer be pertinent. Nevertheless, until new evidence emerges revisiting many of the issues raised in this guideline, the DSG agreed that the current recommendations apply.

Additionally, most of these older studies did not address toxicity or quality of life. This is particularly pertinent for studies where higher intensities of therapy were being investigated. It is very possible that higher intensity therapies may prolong life, but at a significant cost in terms of quality of life, such that patients and physicians should have this information available to be able to make informed choices amongst the therapeutic options. It is strongly recommended that future studies in patients with brain tumours include measures of toxicity and quality of life.

Post-operative radiotherapy as an appropriate recommendation for patients is well supported by randomized studies and remains standard therapy. With regard to the dose issue, only the Medical Research Council (UK) study of 60 Gy in 30 fractions compared with 45 Gy in 20 fractions showed a small statistically significant benefit for the higher dose. No other randomized studies of dose escalation have shown any benefit compared with conventional doses in the range of 50 to 60 Gy. For this reason, the DSG felt that doses in the range of 50 to 60 Gy with conventional fraction sizes were acceptable, particularly in view of the fact that higher doses are likely associated with higher toxicity and increased costs and inconvenience for the patient, in a disease which remains incurable.

The hypofractionated dose utilized in the study by Glinski given over three months is an extremely unusual fractionation, and one that the DSG does not recommend.

All other studies of hyperfractionation, radiation sensitizers, or particle therapy have thus far failed to demonstrate a benefit, and these approaches remain within the domain of experimental therapy. In view of the poor results of conventional

radiotherapy in this disease, the DSG recommends that patients be encouraged to participate in properly conducted experimental studies.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 65 practitioners in Ontario (13 medical oncologists, 15 radiation oncologists, 22 surgeons, one hematologist, and one pathologist). The survey consisted of 21 items evaluating the methods, results, and interpretive summary used to inform the draft recommendations outlined and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey have been reviewed by the Neuro-Oncology Disease Site Group.

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. The guideline has been approved by the Neuro-Oncology Disease Site Group and the Practice Guidelines Coordinating Committee.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Please note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary. The recommendations that follow are based on the previous version of the guideline.

- Postoperative external beam radiotherapy is recommended as standard therapy.
- The high-dose volume should incorporate the enhancing tumour plus a limited margin (e.g., 2 cm) for the planning target volume, and the total dose delivered should be in the range of 50 to 60 Gy in fraction sizes of 1.8 to 2.0 Gy.
- Radiation dose intensification and radiation sensitizer approaches are not recommended as standard care.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and meta-analyses.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Five of six randomized studies demonstrated that postoperative radiotherapy improves survival compared with no radiation in patients with malignant glioma.
- Seven of eight randomized studies of hyperfractionated versus conventionally fractionated radiotherapy demonstrated no significant survival benefit for hyperfractionated radiotherapy. No randomized trials have examined survival following doses in the 50 to 60 Gy range.
- A high-dose volume incorporating the enhancing tumour plus a limited margin (e.g., 2 cm) has achieved similar survival to volumes incorporating whole brain for part or all of the treatment in two randomized studies.
- Radiation dose intensification and radiation sensitizer approaches have not demonstrated survival rates superior to those seen with conventionally fractionated doses of 50 to 60 Gy in randomized studies.

POTENTIAL HARMS

- Radiotherapy has long been recognized to cause possible significant deleterious effects on normal brain tissue. Common acute effects include alopecia, scalp erythema, serous otitis media, nausea, and fatigue. Late effects include radiation necrosis, dementia, and effects on higher cognitive functioning. Many of these clinical late effects can be related to white matter changes noted on magnetic resonance imaging and computed tomography. One study found that the severity and frequency of white matter injury was statistically associated with increasing radiation dose in a phase I/II dose-seeking trial of hyperfractionated cranial radiotherapy.
- In view of the high rate of recurrence at the original site in patients treated with malignant gliomas of the brain, many of the reviewed therapies in this guideline deal with strategies to increase the radiation dose either directly or through mechanisms of radiation sensitization. Inherent in these strategies is a possible increased risk of radiation damage to nearby normal brain structures, which would be associated with toxicity or even shortened survival. Radiation toxicity can sometimes be very difficult to ascertain in patients with glioblastoma multiforme for two reasons: the short median survival of less than one year is probably not long enough for late radiation toxicity to be expressed in many of these patients, and these tumours are

associated with large zones of necrosis which may obscure radiation damage both on imaging studies and at autopsy.
- Patients with anaplastic-atypical astrocytoma have a median survival of approximately three years and represent a group of patients related to the more aggressive neoplasms discussed in this guideline and for whom the same types of experimental treatments have been attempted. One study compared three cohorts of patients treated on different Radiation Therapy Oncology Group (RTOG) protocols with photons alone, photons with chemotherapy, and photons with a neutron boost. The survival rates for these three cohorts were 3.0 years, 2.3 years, and 1.7 years, respectively. This finding suggests that more aggressive treatments were associated with a decrease in survival, and serves as a warning that in future studies patients should be made aware of the possible increased risks of adverse events that may be associated with a decrease in survival over conventional therapy.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- For patients older than age 70, preliminary data suggest that the same survival benefit can be achieved with less morbidity using a shorter course of radiotherapy. This is now being tested in a Canadian randomized study, and patients are encouraged to participate.
- Since the outcome following conventional radiotherapy is so poor for patients older than age 70 with a poor performance status, supportive care alone is a reasonable therapeutic option in these patients.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Neuro-oncology Disease Site Group. Laperriere N, Perry J, Zuraw L. Radiotherapy for newly diagnosed malignant glioma in adults [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Jan [online update]. 25 p. (Practice guideline report; no. 9-3). [80 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2000 Sep 19 (revised 2004 Jan)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Neuro-oncology Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Neuro-Oncology Disease Site Group disclosed potential conflict of interest information.

GUIDELINE STATUS

Please note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary.

GUIDELINE AVAILABILITY

Electronic copies of the updated guideline: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Radiotherapy for newly diagnosed malignant glioma in adults. Summary. Toronto (ON): Cancer Care Ontario. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995 Feb;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on May 14, 2004. The information was verified by the guideline developer on June 2, 2004.

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